TABLE 10.—Continued

Author, year of study, location, reference	Number and type of population	Findings	
Khosla, 1964, Port Talbot, United Kingdom (*1971*)	7,701 males employees in the steel industry	Adjusted mean FEV_1 level (liters)	
		Never smokers	3.70
		Current smokers	
		< 15 cigarettes/day	3.57
		15–24 cigarettes/day	3.48
		25–34 cigarettes/day	3.41
		≥ 35 cigarettes/day	3.37
Schlesinger et al., 1968, Israel (*1972*)	4,331 male civil servants, aged 45 or older	Mean value of the FEV_1/FVC ratio	
		Nonsmokers	76.0
		Ex-smokers	74.3
		Current smokers	
		1–19 cigarettes/day	73.9
		≥ 20 cigarettes/day	72.7
Kesteloot et al., 1968–1969, Belgium (*1976*)	4,961 males in the Belgian military, aged 15 to 59	By multiple regression, FEV_1 reduced by 0.14 liters in smokers of 1–19 cigarettes daily and by 0.23 liters in smokers of 20 or more daily	
O'Donnell and de Hamel, 1969–1970, New Zealand (*1976*)	1,079 male public servants, up to age 65	Reduced mean FEV_1 in smokers of 10 or more cigarettes daily; increased prevalence of FEV_1 below 80 percent of predicted in smokers of more than two packs daily	
Linn et al., 1973, San Francisco and Los Angeles, U.S. (*1976*)	644 male and female office workers, aged 17 to 60	By analysis of covariance, significant reduction of FEV_1 in smokers compared with nonsmokers	
Endelman et al., year not stated, Baltimore, U.S. (*1966*)	410 male volunteers, aged 20 to 103	By partial regression analysis, significant reduction of FEV_1 in current and former cigarette smokers	

TABLE 10.—Continued

Author, year of study, location, reference	Number and type of population	Findings		
Woolf and Suero, year not stated, Toronto (*1971*)	298 female volunteers employed at commercial firms, aged 25–54	Adjusted mean levels		
			FEV_1	FEV_1/FVC ratio
		Nonsmokers	2.65	86.7
		Ex-smokers	2.64	85.0
		Current smokers		
		70 cigarettes/week	2.63	85.2
		71–140 cigarettes/week	2.50	85.1
		≥140 cigarettes/week	2.45	84.1
Krumholz and Hedrick, year not stated, Dayton, U.S. (*1973*)	227 male executives, aged 35–64, selected to include nonsmokers (n=136) and long-term smokers (n=91)	Mean values		
			FEV_1	FEV_1/FVC
		Nonsmokers	3.80	77.3
		Smokers	3.42	73.6
Grimes and Hanes, year not stated, Los Angeles, U.S. (*1973*)	1,059 male and female insurance company employees	By multiple regression, significant reduction of FEV_1 level in male smokers but not in female smokers		
Lefcoe and Wonnacott, year not stated, western Ontario, Canada (*1974*)	1,072 males in four occupational groups	By multiple regression, significant reduction of FEV_1 in current cigarette smokers		
Higgenbottam et al., year not stated, London, England (*1980*)	18,403 male civil servants, aged 40 to 64	Reduced FEV_1 in cigarette smokers compared with nonsmokers, increased effect with increasing daily amount in current smokers		

(Table 10), even though people with symptomatic airflow obstruction may be likely to retire from their jobs.

Recently, predictors of the incidence of airflow obstruction have been examined with multivariate techniques in data from population samples in Tecumseh, Michigan (Higgins et al. 1982), and in Tucson, Arizona (Lebowitz et al. 1984). In Tecumseh, the strongest predictors of airflow obstruction (defined as an FEV_1 less than 65 percent of predicted) were age, the number of cigarettes smoked daily, changing smoking habits, and the initial FEV_1 level (Higgins et al. 1982). The addition of other variables to the predictive model did not greatly improve its validity. In Tucson, these same variables, along with certain symptoms and illnesses, and skin test reactivity were significant predictors (Lebowitz et al. 1984). During the 10 years of followup of a population sample in Finland, incidence cases of chronic airflow obstruction (defined as FEV_1/FVC ratio less than 60 percent) were observed only in those who continued to smoke (Huhti and Ikkala 1980). These studies of incidence highlight the importance of cigarette smoking in the etiology of airflow obstruction; new cases are rare among nonsmokers.

Dose–Response Relationships

Dose–response relationships between FEV_1 level and the amount of cigarette smoking have been described with simple descriptive statistics and further characterized by multiple regression analysis. In cross-sectional data, the FEV_1 level varies inversely with the amount smoked. Although the variation in mean FEV_1 levels among strata of smoking appears clinically unimportant, the distributions of values in smokers and nonsmokers are quite different (Figure 4). Cigarette smokers more often have abnormal lung function, regardless of the criteria applied to the population (Mueller et al. 1971; Knudson et al. 1976; Burrows et al. 1977a; Detels et al. 1979; Rokaw et al. 1980; Beck et al. 1981). This increased prevalence of abnormal function is a result of the skewed distribution of function in smokers, with a subgroup of the smokers showing a large decline rather than the entire group shifting by a small amount (Figure 4). As noted in this reference, however, there are decreasing numbers of smokers with FEV_1 above the mean for nonsmokers as pack-years increase, suggesting that all smokers are probably somewhat affected, even though only a minority eventually develop clinically significant airflow limitation.

In several populations, the relationship between cigarette smoking and FEV_1 level has been examined in greater detail. Burrows et al. (1977a) used linear multiple regression analysis to examine the relationship between cigarette smoking and ventilatory function in a population sample in Tucson, Arizona. Pack-years, a cumulative-dose measure, was the strongest predictor of FEV_1 level among the

smoking variables considered. In currently smoking men and women, the FEV_1 declined by approximately 0.25 percent of the predicted value for each pack-year of cigarette smoking; the effect was of a similar magnitude in ex-smokers. Using data from three separate U.S. communities, Beck and colleagues (1981) assessed the importance of six separate smoking variables: amount smoked daily, use of filters, inhalation, age started, age stopped for ex-smokers, and cumulative pack-years. For the FEV_1, the strongest predictors in male current smokers were the duration of smoking and the amount smoked; in female current smokers, only pack-year was statistically significant. The number of years of cessation was associated with FEV_1 in male but not in female ex-smokers.

However, in both the multiple regression analysis reported by Beck et al. (1981) and that reported by Burrows et al. (1977a), the measured cigarette smoke variables accounted for only about 15 percent of the variation of age- and height-adjusted FEV_1 levels. Unmeasured aspects of cigarette smoking, other environmental exposures, and the characteristics of the smokers must contribute to the unexplained variation. A role for the type of cigarette smoked has not yet been established (USDHHS 1981), and the impact of differences in depth or pattern of inhalation and other aspects of the pattern of smoking remains to be investigated; they are discussed in more detail in the chapter on low tar and low nicotine cigarettes. Further studies of these aspects of cigarette smoking are needed to monitor the consequences of changing cigarettes.

Factors Other Than Cigarette Smoking

A number of risk factors other than cigarette smoking have been postulated as contributing to the development of airflow obstruction (Table 7). Of these, a definite role for α_1-antitrypsin deficiency has been established, but only the small number of persons with homozygous deficiency incur markedly increased risk (Morse 1978). The current hypotheses on susceptibility to cigarette smoke postulate roles for childhood respiratory illnesses (USDHEW 1979; Burrows and Taussig 1980; Samet et al. 1983), for endogenously determined hypersensitivity of the lung, and for other genetic and familial factors (Speizer and Tager 1979; USDHHS 1980a). At present, these hypotheses remain largely untested. The data are similarly incomplete at present for the other factors listed as putative risk factors in Table 7. The status of each is briefly reviewed below.

ABH Secretor Status

Secretion of ABH antigens is a genetically determined trait that follows an autosomal dominant inheritance pattern; approximately

70 to 80 percent of the population excrete antigen into the body fluids (Cohen et al. 1980a). In a genetic-epidemiology study in Baltimore, Maryland (Cohen et al. 1980a), ABH nonsecretors had lower levels of FEV_1/FVC ratio and a higher proportion with FEV_1/FVC ratio below 69 percent. Studies in France (Kauffmann et al. 1982a, 1983) and in England (Haines et al. 1982) have confirmed reduced expiratory flow rates in ABH nonsecretors. In contrast, ABH secretor status did not predict the development of obstructive airways disease in the Tecumseh, Michigan, population (Higgins et al. 1982).

Air Pollution

Although exposure to air pollution at high levels may exacerbate the clinical condition of persons with chronic lung disease, a causal role for air pollution in the development of airflow obstruction has not been established (Tager and Speizer 1979; USDHHS 1980b). However, smoking is the major predictor for chronic airflow obstruction in areas of high as well as low atmospheric air pollution.

Airways Hyperreactivity

Orie and colleagues in the Netherlands (Orie et al. 1960) speculated that bronchial hyperreactivity and allergy may predispose to asthma and chronic bronchitis. Findings from two small longitudinal studies have suggested that airways reactivity may influence individual susceptibility to cigarette smoke. Barter and colleagues followed 56 patients with mild chronic bronchitis during a 5-year period (Barter et al. 1974; Barter and Campbell 1976). The rate of decline of FEV_1 increased with the degree of airways reactivity, as measured by reversibility with isoproterenol or responsiveness to methacholine. Britt et al. (1980) measured change of FEV_1 in 20 young adult male relatives of patients with chronic obstructive pulmonary disease. The decline of FEV_1 was approximately five times larger in the nine subjects with a positive methacholine challenge test. In patients with clinically diagnosed airflow obstruction, airways reactivity is also associated with more rapid decline of lung function (Kanner et al. 1979). Because airway reactivity would affect the FEV_1 directly as well as possibly influence the susceptibility to smoke, it is difficult to ascertain from these data whether the relationship between airway reactivity and COLD is direct or spurious.

Alcohol Consumption

The epidemiological data on alcohol consumption are conflicting. A study of former alcoholics demonstrated an excess prevalence of lung function abnormalities, including airflow obstruction (Emergil

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and Sobol 1977). In the Tucson population, alcohol consumption was a significant predictor of ventilatory function after the effect of smoking was controlled (Lebowitz 1981). The findings of an investigation in Yugoslavia were similar (Saric et al. 1977). However, two large U.S. investigations did not demonstrate adverse effects of alcohol intake (Cohen et al. 1980b; Sparrow et al. 1983a).

Atopy

Cross-sectional data from the Tucson population suggest increased susceptibility to cigarette smoke in atopic people (Burrows et al. 1976). In subjects aged 15 to 54, the prevalence of an FEV_1/FVC ratio below 90 percent of predicted value increased with skin test reactivity among both smokers and nonsmokers. Subsequent reports from this same study have not confirmed an overall relationship between FEV_1 level and atopy, but indicate that atopy may predispose to airflow obstruction in a subset of the population (Burrows et al. 1977a, 1983). Burrows and coworkers (1981) also reported an increased level of IgE in smokers independent of their allergy skin test reactions, and the interrelationship of these factors is currently being examined.

Childhood Respiratory Illness

In a longitudinal investigation of 792 English working men, Fletcher and coworkers (Fletcher et al. 1976) found a cross-sectional association between childhood illness history and FEV_1 level. The decline of FEV_1 level during the study's longitudinal phase was not correlated with childhood illness variables. In contrast, analyses of cross-sectional data from a population sample in Tucson suggested that childhood respiratory illnesses may increase susceptibility to cigarette smoke (Burrows et al. 1977b). In this population, people with a history of respiratory trouble before age 16 demonstrated excessive decline of ventilatory function with increasing age and with increasing cigarette consumption.

Familial Factors

Familial aggregation of lung function level, adjusted for age, height, and sex, has been demonstrated in populations in the United States and elsewhere (Higgins and Keller 1975; Tager et al. 1976; Schilling et al. 1977; Mueller et al. 1980). However, a recent report suggests that the familial aggregation of lung function may be a reflection of the familial aggregation of body habitus (Lebowitz et al. 1984). Relatively modest correlations of FEV_1 level have been demonstrated between siblings and between parent–child pairs. The role of familial factors is further supported by investigations demonstrating increased prevalence of airflow obstruction in rela-

tives of diseased subjects (Kueppers et al. 1977; Tager et al. 1978; Cohen 1980). This familial factor cannot be explained by familial resemblance of α_1-antitrypsin phenotype or of ABH secretor status (Kueppers et al. 1977; Cohen 1980). In the Tecumseh population, however, family history of airflow obstruction did not predict the incidence of this disease. The results of twin studies are also consistent with genetic influences on FEV_1 level and suggest that genetic factors may influence susceptibility to cigarette smoke (Webster et al. 1979; Hankins et al. 1982; Hubert et al. 1982).

Occupation

Several population-based investigations suggest that occupational exposures other than those recognized as causing lung injury may have some effect on lung function level. In Tecumseh, mean age and height-adjusted FEV_1 scores in men were highest in farmers and lowest in laborers; the differences were not explained by smoking and were present in nonsmokers (Higgins et al. 1977). Similarly, in Tucson, men reporting employment in certain high risk industries or exposure to specific harmful agents had a higher prevalence of abnormal lung function (Lebowitz 1977a). In a Norwegian case–control study, men employed in workplaces characterized as polluted were at increased risk for clinically diagnosed emphysema (Kjuus et al. 1981). Longitudinal studies of industrial populations also show that occupational exposures may increase the rate of decline of FEV_1 (Jedrychowski 1979; Kauffmann et al. 1982b; Diem et al. 1982). For example, Kauffmann et al. (1982b) found that FEV_1 change during a 12-year period varied with job exposures in an employed industrial population. Effects of dust, gas, and heat were present, as was evidence for a dose–response relationship between increasing exposure and a greater rate of decline. In these studies, however, smoking effects were generally much greater than the occupational effects.

Passive Exposure to Tobacco Smoke

Passive exposure is discussed in detail elsewhere in this Report.

Respiratory Illnesses

In an 8-year followup study of London men, chest infections were not associated with a rate of FEV_1 decline (Fletcher et al. 1976). The findings of several smaller longitudinal studies were similarly negative with regard to respiratory infection (Howard 1970; Johnston et al. 1976). It is now apparent that mucus hypersecretion and airflow obstruction are separate pathophysiological entities that have a common cause—cigarette smoking (Fletcher et al. 1976; Peto et al. 1983).

Socioeconomic Status

Weak effects of socioeconomic status on lung function level have been demonstrated in community samples in Tecumseh (Higgins et al. 1977) and in Tucson (Lebowitz 1977b). In both populations, lung function appeared to be influenced independently by socioeconomic status indicators, even after controlling for cigarette smoking. In the Tecumseh study, FEV_1 increased slightly with increasing income and education level (Higgins et al. 1977); in the Tucson study, the proportion of people with an abnormal FEV_1 varied in a similar pattern with these indices (Lebowitz 1977a). Effects of socioeconomic status were present in nonsmokers in both investigations. Stebbings (1971), in a sample of nonsmokers in Hagerstown, Maryland, also demonstrated an association between lung function level and socioeconomic status.

In summary, there is evidence that a number of factors other than cigarette smoke may influence lung function, but the influence of these factors is small relative to the effect of smoking, and the major question is whether they can influence susceptibility to cigarette-induced lung injury rather than whether they, of themselves, result in lung disease in nonsmokers.

Development of Airflow Obstruction

At this time, the natural history of airflow obstruction has been only partially described; a population has not yet been followed from childhood to the development of airflow obstruction during adulthood. However, the available data from separate investigations cover the entire course of the disease and support the conceptual model proposed in Figure 15.

With aging, measures of function begin to deteriorate after age 25 to 30. In nonsmokers without respiratory disease, cross-sectional data generally show that the FEV_1 declines by 20 to 30 ml per year (Dickman et al. 1969; Morris et al. 1971; Cotes 1979; Crapo et al. 1981). Longitudinal data have been confirmatory (Tables 11 and 12). For example, Tockman (1979) measured the FEV_1 loss during an 8-year period in 399 male nonsmokers. In most, the FEV_1 declined at 25 ml annually; a few, with an initial FEV_1 lower than 2.5 l, lost 34 ml annually.

Sufficient excessive loss leads to the development of airflow obstruction. However, many questions remain unanswered concerning this process of functional deterioriation. It is unclear whether the loss always occurs uniformly or if it develops in stages with intermittent and relatively steep declines (Bates 1979; Burrows 1981). The concept that the decline is nearly always gradual receives strong support from the findings of the 8-year longitudinal study conducted by Fletcher and coworkers (1976). In this investigation of

TABLE 11.—Association between cigarette smoking and longitudinal change in lung function in selected population samples

Author, years of study, location, reference	Number and type of population	Findings		
Higgins and Oldham, 1954–1959 Rhondda Fach, Wales (*1962*)	253 male miners, ex-miners, and nonmining controls	Annual decline of indirect maximal breathing capacity (liters/min)		
			Controls	Miners, ex-miners without pneumoconiosis
		Nonsmokers	1.6	0.8
		Ex-smokers	0.7	1.8
		Current smokers		
		1–14 g/day	1.3	1.7
		≥ 15g/day	1.6	2.2
Ashley et al., 1958–1968, Framingham, U.S. (*1975*)	399 men and 636 women, aged 37 to 69 in 1958	10-year change in FEV_1/FVC ratio (age-standardized to overall distribution for each sex)		
			Men	Women
		Nonsmokers	0.21	−3.6
		Continued smokers	−1.3	−4.1
		Stopped, 1958–1968	0.51	−4.6
Higgins et al., 1957–1966, [illegible]tavely, England (1968b)	594 men, aged 25–34 or 55–64 in 1957	Annual decline of $FEV_{75\%}$ (ml/year) by age and smoking in 1957		
			25–34 yrs	55–64 yrs
		Nonsmokers	21	32
		Ex-smokers	29	44
		Current smokers		
		1–14g/day	37	54
		≥ 15g/day	38	37

TABLE 11.—Continued

Author, years of study, location, reference	Number and type of population	Findings		
Huhti and Ikkala, 1961–1971, Harjavalta, Finland (*1980*)	492 men and 671 women, aged 40 to 64 in 1961	Annual decline of FEV_1 (ml/year)	Men	Women
		Nonsmokers	33	27
		Ex-smokers	45	27
		Continued smokers	44	39
		Stopped, 1961–1971	51	35
Wilhelmsen et al., 1963–1967, Göteborg, Sweden (*1969*)	313 men, aged 50 in 1963	Annual decline of FEV_1 (ml/year)		
		Nonsmokers	43	
		Ex-smokers	33	
		Current smokers		
		1–14g/day	70	
		≥15g/day	70	
		Stopped, 1963–1967	40	

Author, years of study, location, reference	Number and type of population	Findings		
Oxhoj et al., 1963–1973, Goteborg, Sweden (same population as Wilhelmsen et al. 1969) (*1976*)	269 men, aged 50 in 1963	Annual decline of FEV_1 (ml/year)		
		Nonsmokers	40	
		Ex-smokers	37	
		Current smokers	58	
		Stopped, 1963–1973	49	
Van der Lende et al., Vlaardingen, 1967–1978, and Vlagtwedde, 1967–1976, Netherlands (*1981*)	894 men and women, aged 25 and older	Mean annual decline of FEV_1	Unadjusted	Adjusted
		Nonsmokers	13.3	16.6
		Ex-smokers	15.8	13.4
		Pipe/cigar	24.4	22.6
		< 4 g/cig	3.6	8.7
		5–14 g/cig	22.2	20.9
		15–24 g/cig	31.4	28.2
		≥ 25 g/cig	35.8	34.0
Krzyzanowski, 1968–1973, Cracow, Poland (*1980*)	2,572 men and women, aged 19 to 70	Annual decline of FEV_1 (ml/year)	Men	Women
		Nonsmokers	56	44
		Continued smokers	73	53

TABLE 12.—Association between cigarette smoking and longitudinal change in lung function in selected occupational or other groups

Author, years of study, location, reference	Number and type of population	Findings	
Comstock et al., 1962–1963 to 1967 or 1969, various locations U.S. (*1970*)	670 male telephone company employees, aged 40 to 65	Decline in FEV_1 (liters) between surveys	
		Nonsmokers	0.28
		Ex-smokers	0.17
		All smokers	0.41
Howard, 1956 to 1967, Sheffield, England (*1970*)	159 male employees of an engineering works	Annual decline in $FEV_{75\%}$ (ml/year)	
		Nonsmokers	0.036
		Ex-smokers	0.025
		Current smokers	0.031
DeMeyere and Vuylsteek, 1967 to 1970, Ghent, Belgium (*1971*)	627 male railroad workshop employees	Annual decline in FEV_1 (ml/year)	
		Nonsmokers	92
		Ex-smokers	96
		Current smokers	
		1–14 g/day	96
		≥15 g/day	88
		Stopped, 1961–1971	80

TABLE 12.—Continued

Author, years of study, location, reference	Number and type of population	Findings	
Fletcher et al., 1961 to 1969, London, England (*1976*)	792 male transport maintenance or bank workers, aged 30 to 59 at entry	Annual decline of FEV_1 (ml/year)	
		Nonsmokers	36
		Ex-smokers	31
		Continued smokers	
		< 5 cigs/day	44
		5–15 cigs/day	46
		15–25 cigs/day	54
		≥ 25 cigs/day	54
Kauffmann et al., 1960 to 1972, Paris, France (*1979*)	575 male factory workers, aged 30 to 54 in 1960	Annual decline of FEV_1 (ml/year), adjusted for initial level	
		Nonsmokers	40
		Ex-smokers	44
		Current smokers	
		< 15 g/day	46
		≥ 15 g/day	51
Jedrychowski, 1968 to 1973, Cracow, Poland (*1979*)	186 male employees of a fertilizer factory	5-year decline of FEV_1 as percent of mean, by 1973 smoking	
		Nonsmokers	3
		Ex-smokers	5
		Current smokers	7
Poukkula et al., 1967 to 1977, Oulu, Finland (*1982*)	659 male pulp mill employees, aged 18 to 64 in 1967	Annual decline of FEV_1 (ml/year)	
		Nonsmokers	37
		Ex-smokers	39
		Continued smokers	49
		Stopped, 1967-1977	48

TABLE 12.—Continued

Author, years of study, location, reference	Number and type of population	Findings	
Woolf and Zamel, years not given, Toronto, Canada (*1980*)	302 female volunteers, aged 25 to 54 at entry	5-year change in FEV_1 as percent of initial value	
		Nonsmokers	1.5
		Ex-smokers	0.8
		Smokers	
		≤70 cigs/week	-0.4
		71-140 cigs/week	-3.6
		>140 cigs/week	4.6
Bosse et al., 1963–1968 to 1969–1974, Boston, U.S. (*1981*)	850 male volunteers	Annual decline of FEV_1 (ml/year), adjusted for age and initial level	
		Nonsmokers	0.053
		Ex-smokers	0.057
		Current smokers	0.085
Love and Miller, 1957 to 1973 (average followup, 11 years), United Kingdom (*1982*)	1,677 male coalminers	11-year decline in FEV_1 (liters)	
		Nonsmokers	0.41
		Ex-smokers	0.48
		Intermittent smokers	0.52
		Current smokers	0.53

792 employed men, the individual patterns of temporal change of the FEV_1 were strongly variable, but the loss generally occurred gradually. Fletcher et al. further demonstrated that FEV_1 level correlated with FEV_1 slope, a finding that they termed the "horse-racing effect." Correlation between slope and level would be anticipated, if functional loss occurs gradually. This correlation has important implications for intervention; those losing FEV_1 more rapidly should become identifiable early as they develop a reduced FEV_1 level. Other studies, however, do not agree with either the pattern of FEV_1 decline or the "horse-racing" effect. Rapid declines to levels compatible with clinical disease or followed by a prolonged plateau have been described (Howard and Astin 1969; Howard 1970; Johnston et al. 1976). In a followup study of Canadian men with chronic bronchitis, steep declines of FEV_1 without subsequent improvement were frequently observed (Bates 1973). Additionally, correlation of FEV_1 level and slope has been found in most other longitudinal investigations (Howard 1970; Petty et al. 1976; Huhti and Ikkala 1980; Bosse et al. 1981; Clement and van de Woestijne 1982; Kauffmann et al. 1982b), but not in all (Barter et al. 1974; Krzyzanowski 1980).

Another unanswered question concerning functional deterioration is whether gradual decline occurs in a linear or a nonlinear fashion (Fletcher et al. 1976). Sufficient numbers of people have not yet been followed to distinguish alternative patterns, although the available data indicate acceleration of the decline with aging (Emergil et al. 1971; Fletcher et al. 1976).

In spite of these uncertainties concerning the development of airflow obstruction, the available data indict cigarette smoking as the primary risk factor for excessive loss of FEV_1 (Tables 11 and 12). The findings in both general population samples (Table 11) and occupational and volunteer cohorts (Table 12) have been similar. Recent reports from Belgium (Bande et al. 1980; Clement and van de Woestijne 1982) and from Connecticut (Beck et al. 1982), not readily summarized in tabular form, also described a strong effect of smoking on FEV_1 decline. A few studies have not shown increased loss in cigarette smokers (Howard 1970; De Meyere and Vuylsteek 1971). Even in people with clinically diagnosed airflow obstruction, continued smoking maintains the excess decline of FEV_1 (Hughes et al. 1982), although not all findings are consistent (Ogilvie et al. 1973; Johnston et al. 1976).

Dose–response relationships have been found in many investigations between the amount smoked during followup and the FEV_1 decline (Tables 11 and 12). The reported increases from the lowest to the highest smoking categories range up to 10 to 15 ml annually. Although this additional loss in heavier smokers appears small, if sustained for long periods of time it would shorten the time interval

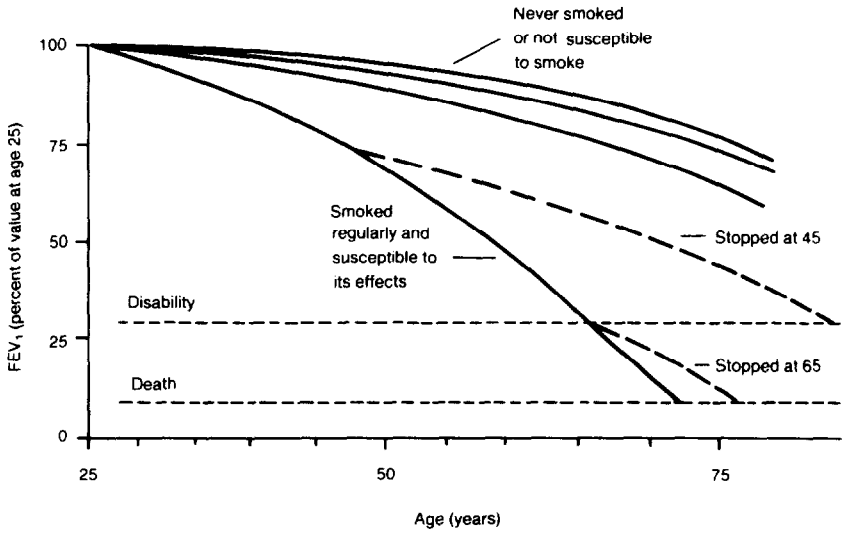

FIGURE 24.—Risks for men with varying susceptibility to cigarette smoke and consequences of smoking cessation

NOTE: + = death.
SOURCE: Fletcher and Peto (1977).

to the development of functional impairment. So far, favorable effects of filter tip smoking and declining tar content on the rate of decline have not been shown (Fletcher et al. 1976; Sparrow et al. 1983b).

Generally, sustained smokers experience a greater loss than those who stop during followup. In the study by Fletcher et al. (1976) of London men, subjects who stopped smoking at the beginning of the followup period lost FEV_1 at the same rate as never smokers. The results of two U.S. studies of ex-smokers are similar (Bosse et al. 1981; Beck et al. 1982). This reduced loss in ex-smokers emphasizes the importance of active smoking and the immediate benefits of smoking cessation (Figure 24). Smokers with reduced FEV_1 may be protected from developing clinically significant loss by timely smoking cessation (Fletcher and Peto 1977).

The distribution of FEV_1 decline has been characterized and described for some populations, including patient groups (Burrows and Earle 1969; Howard 1974; Barter et al. 1974), population samples (Milne 1978), and occupational cohorts (Howard 1970; Fletcher et al. 1976). Similar data are also available for the mid-maximum expiratory flow, another measure of ventilatory function (Bates 1973; Woolf and Zamel 1980). In each of these investigations, the distribution of FEV_1 decline is unimodal (Figure 25); that is, a distinct population with more rapid decline is not sharply separated from those with lesser rates. The modes and medians of the distributions

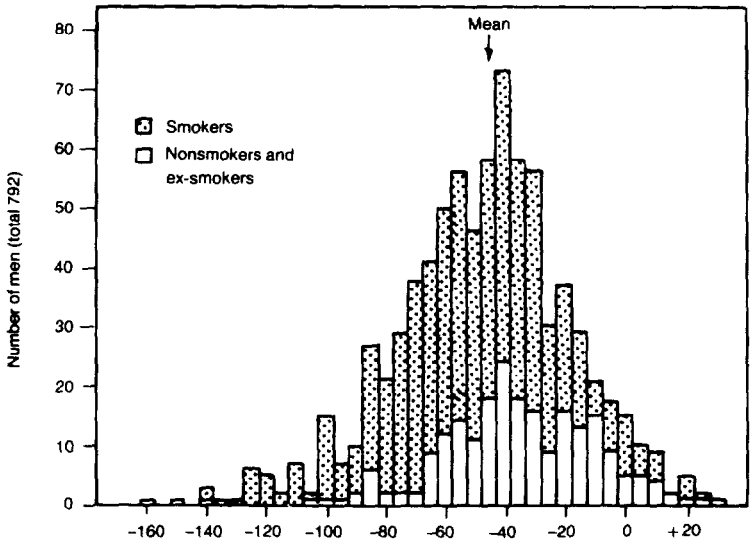

FIGURE 25.—Distribution of 8-year FEV_1 slope in 792 London men

SOURCE: Fletcher et al. (1976).

are generally negative, but some subjects have had positive slopes during the relatively brief followup period of investigations conducted up to this time.

The distributions tend to be skewed by subjects losing FEV_1 more rapidly. The proportion of cigarette smokers is increased among those in the tail of excess loss (Figure 25). For example, Clement and van de Woestijne (1982) examined subjects with excess FEV_1 decline in a prospective study of 2,406 members of the Belgian Air Force. Losses beyond those expected from nonsmokers affected 6 percent of nonsmokers, 7.5 percent of light smokers (<20 cigarettes/day), and 12 percent of heavy smokers (>20 cigarettes/day).

The shape of the distribution of FEV_1 decline has important implications for the development of airflow obstruction. Smokers are not sharply separated from nonsmokers (Figure 25), but more often lose FEV_1 at a rapid rate. Because of this spectrum of severity, not all smokers develop significant airflow obstruction. Although the factors that lead to excessive loss in individual smokers remain uncertain, they may include differences in the pattern of smoking. It is apparent, however, that this susceptible minority can be protected by smoking cessation.

Summary

During the 20 years that have elapsed since the 1964 Surgeon General's Report, the relationship between cigarette smoking and airflow obstruction has been intensively investigated. Surveys of community samples and other groups have established that airflow obstruction is a common condition in the United States and elsewhere. In some populations, as high as 10 percent of adults are affected.

Determinants of lung function level and of the prevalence of airflow obstruction have now been examined in many populations throughout the world. Cigarette smoking is the strongest predictor of abnormal measures of ventilatory function. A causal relationship between cigarette smoking and airflow obstruction is supported by the consistency of the many published reports, the strength of the association, and the evidence for dose–response.

Many risk factors for airflow obstruction other than cigarette smoking have been postulated, including other harmful environmental exposures and the inherent susceptibility of the smoker. Homozygous α_1-antitrypsin deficiency can explain only a minute proportion of the disease burden. The development of airflow obstruction by only a minority of smokers indicates that the interaction of smoking with other factors may influence the risk for specific smokers. Current research emphasizes the potential roles of childhood respiratory illness and airways hyperresponsiveness.

Longitudinal studies have now partially described the prolonged natural history of airflow obstruction. Excessive loss of ventilatory function, beyond that expected from aging alone, results in the development of disease in cigarette smokers. Only a susceptible minority of cigarette smokers lose function at a rate that will eventually cause clinically significant impairment. For this group, timely smoking cessation can prevent the development of disease.

EMPHYSEMA

Introduction

Pulmonary emphysema is frequently present in the lungs of individuals with chronic obstructive lung disease. This section has three purposes: (1) to review the definition, types, and quantification of emphysema; (2) to summarize the physiological and radiographic feature of emphysema; and (3) to discuss critically the relationship of smoking to emphysema, based upon observations in people and in experimental animals. Current concepts of the pathogenesis of emphysema are reviewed elsewhere.

Definition of Emphysema

The generally accepted definition of emphysema is an anatomic condition of the lung characterized by abnormal dilation of air spaces distal to the terminal bronchioles accompanied by destruction of air space walls (American Thoracic Society 1962; Heard et al. 1979). Difficulties with this definition have been discussed by Thurlbeck (1983). Normal air space dimensions have not been determined, and criteria of destruction have not been defined. These limitations hamper attempts to investigate the earliest lesions of emphysema and the subtle effects of environmental agents on lung structure.

Types of Emphysema

British pathologists pointed out in the forties and fifties that emphysematous lesions in certain people involved the respiratory bronchioles, which appeared as grossly enlarged airspaces in the center of the primary lung lobules surrounded by normal lung. In other individuals, the alveolar ducts were involved early, and even mild involvement appeared grossly as a coarsening of the architecture of the entire lobule. They designated the two polar patterns of emphysema as centrilobular emphysema (CLE) and panlobular emphysema (PLE) (Heppleston and Leopold 1961). Many lungs either show both types of emphysema or are unclassifiable. Of 122 lungs with emphysema examined by one pulmonary pathologist, 73 were considered mixed or unclassifiable and 49 were clearly CLE or PLE (Mitchell et al. 1970). When the agreement of three pathologists was required, only 27 of the original 122 lungs remained classifiable and 95 were mixed or could not be classified. There were no statistically significant differences between the groups classified as PLE or CLE in any clinical variables. The only nonsmokers in either group had CLE, and the proportion of light smokers (less than 25 pack-years) was very similar between groups. In this study and others (Anderson and Foraker 1973), CLE was most severe in the upper lobes and PLE was uniformly distributed. According to Thurlbeck (1976), a common

combination is CLE in the upper lobes and PLE in the lower lobes; where lobectomies are used for correlation, typing of emphysema is therefore a particularly empty exercise. When emphysema is far advanced, it is often impossible to recognize the site of the initial involvement. Thus, it is not clear whether the differences in prevalence of CLE and PLE are real or represent differences in interpretation by different observers.

Several localized types of emphysema occur in areas around scar tissue (paracicatricial), along interlobar and interlobular septa (paraseptal), and as bullous lesions (which represent the most advanced and extreme distortion of normal lung structure). Bullous deformities occur with any type of emphysema, including CLE and PLE. Occasionally, bullous lesions occupy huge intrapulmonary volumes.

Detection of Emphysema

The detection of emphysema requires suitably prepared lung specimens. At a minimum, this means the lung must be fixed in inflation (Thurlbeck 1964). Fume fixation or fixation by instillation of liquid fixative through the airways is satisfactory, but for optimal evaluation of the latter group, barium impregnation or paper-mounted whole-lung sections should be used. Because lungs with emphysema frequently also have some degree of intrinsic airways disease, the severity of emphysema and the clinical state of the patient may not correlate directly. Pathologists can easily recognize mild degrees of emphysema that are rarely associated with clinical disability.

Quantification of Emphysema

There are a number of techniques for quantifying the volume of lung involved with "obvious" emphysema that are adequately reproducible and correlate well with one another (Thurlbeck 1976; Bignon 1976). Semi-quantitative or subjective scoring methods as well as point counting have been used. These approaches all require lungs inflated to a relevant volume, usually one approximating total lung capacity during life. This can be achieved by a distending pressure of 25 cm H_2O (Thurlbeck 1979; Berend et al. 1980).

In the scoring method, the lung is divided into a number of units and the severity of emphysema in each unit is scored (mild, moderate, or severe receive 1, 2, or 3 points, respectively). The scores for each unit are summed to give a total score for the lung (Ryder et al. 1969). Alternatively, lung slices may be matched by visual comparison to a set of graded standards to achieve an emphysema score (Thurlbeck et al. 1970). These methods include both severity and extent of emphysema, and although they involve subjective judgments, they have proved to be remarkably reproducible.

In the point counting approach, regularly spaced points are superimposed on a lung slice. Each point is recorded as falling on normal parenchyma, emphysematous parenchyma, or nonparenchyma (conducting airways or vessels). The volume proportion of emphysematous lung is recorded. This method can be objective (e.g., if an emphysematous space is taken to be one greater than 1 mm in diameter), but it includes only extent and not severity of emphysema.

Morphometric methods carried out on histologic sections, exemplified by the mean linear intercept (Lm) (Thurlbeck 1967a, b), are strictly objective, but they require careful attention to problems of sampling and are time consuming and insensitive to focal disease. For measurements of the Lm, histologic sections are made of blocks selected by stratified random sampling. The average distance between alveolar walls is determined from the number of intersections of alveolar walls with a line of known length. The internal surface area of the lung can be calculated when the volume of the lung is known (Hasleton 1972).

Pulmonary Function in Emphysema

Because unequivocal proof of the presence of emphysema requires direct examination of lung tissue, the strategies used to characterize the pulmonary function abnormalities associated with emphysema have either involved comparison of functional data collected during life with autopsy or surgical material or have used measurements made exclusively on post-mortem specimens. Two important conclusions from these studies should be noted at the outset. First, impaired air flow during maximal expiratory maneuvers, as reflected in reduced values for the FEV_1, $FEV_{1\%}$, and $FEF_{25-75\%}$, is neither sensitive nor specific for emphysema. It is possible to have severe emphysema without clinical obstructive lung disease (Thurlbeck 1977). It is also possible to have severe chronic obstructive lung disease without having emphysema, even though most patients with advanced chronic obstructive lung disease have some degree of emphysema (Mitchell et al. 1976). Second, none of the tests used to identify early obstructive lung disease, such as closing volume, the single breath N_2 curve, or frequency dependence of compliance, distinguish diminished elastic recoil that may be related to emphysema (see below) from increased resistance in small airways (Buist and Ducic 1979). Even the determination of density dependence of maximum expiratory airflow, once felt to be specific for detecting abnormalities in the caliber of small airways, is not immune to the effects of lung elastic recoil. A decreased effect on maximal expiratory air flow of using low density gas can be caused by decreased elastic recoil (Gelb and Zamel 1981).

Pulmonary function testing of individuals with proven emphysema often shows increases of residual volume, functional residual capacity, and total lung capacity and decreases of maximal expiratory air flow (Boushy et al. 1971; Park et al. 1970; reviewed in Kidokoro et al. 1977). However, because individuals with emphysema commonly also have intrinsic airway disease (Cosio et al. 1978) affecting the results of these pulmonary function tests in the same direction as emphysema, it is clear that these tests are not specific for emphysema. Accordingly, there has been interest in other, more distinctive tests. Among readily applicable tests, the diffusing capacity has proved to be directly related to the extent of emphysema (Park et al. 1970; Boushy et al. 1971; Berend et al. 1979), presumably reflecting a diminution of internal surface area available for gas exchange. The usefulness of the diffusing capacity to identify and estimate emphysema is limited, however, because the measurement is not sensitive to low grades of emphysema (Symonds et al. 1974) or specific for emphysema. Moreover, the results must be interpreted carefully in smokers because the values for diffusing capacity are lower than in nonsmokers, and the difference extends even to young smokers who are not likely to have emphysema (Enjeti et al. 1978; Miller et al. 1983).

Mechanical Properties of the Lungs in Emphysema

Measurements of the pressure–volume characteristics of the lung have generally been regarded as a reliable means of physiologically detecting and quantifying emphysema because (a) patients with emphysema often have increased lung distensibility and correspondingly low transpulmonary pressures (loss of elastic recoil) and (b) the severity of emphysema has seemed to correlate with the change in elastic recoil. It has also been assumed that the regions of lung with emphysema are the cause of the decreased lung elastic recoil, an assumption that appears reasonable because elastic recoil results in part from surface forces at the air-liquid interface and there is less surface area in emphysema.

Recent observations challenge these concepts. Berend and Thurlbeck (1982), using lungs obtained post mortem, could not demonstrate a relationship between indices of lung elasticity and the grade of emphysema in 48 lungs ranging in grade from 2 to 80 (on a scale of 100), and observed (Berend et al. 1981) in emphysematous lungs that the relative increase in compliance of the lower lobes was greater than the upper lobes, even though the emphysema was worse in the upper lobes. Others have also reported poor correlations between emphysema and elastic recoil. Silvers et al. (1980) found decreased elastic recoil and increased total lung capacity in excised human lungs with minimal emphysema, and Schuyler et al. (1978) noted in hamsters given small doses of elastase intravenously that there was

decreased lung elastic recoil at low lung volumes, although the lungs did not show morphometric changes. Guenter et al. (1981) noted that mild emphysema produced by pepsin caused greater changes in lung elasticity than similar degrees of lung destruction produced by endotoxin-induced repetitive leukocyte sequestration. They suggested that these differences may be due to differences in the location of the connective tissue injury within the lung.

Even among those who have reported an association between emphysema and elastic recoil, the correlations have been best when the emphysema was severe (Greaves and Colebatch 1980). Pare et al. (1982) found a correlation between emphysema grade and elastic properties of the lungs in 55 persons; however, in 5 whose surgically removed lung tissue received emphysema scores between 20 and 70 (out of a maximum of 100), the elastic properties of the lungs tested preoperatively were indistinguishable from normal. While such discrepancies probably reflect the limitations of relating the overall elastic properties of both lungs to the morphology of a single lobe, it must also be recognized that the sensitivity of the pressure–volume diagram is limited, since a narrow range of pressure (to 20 cm H_2O) depicts the average retractive force from millions of air spaces and the connective tissue network of the lung.

From these recent findings it must be concluded that the relationship between elastic recoil and morphologic measures of emphysema is not highly predictable, and that the decrease of elastic recoil and increase of total lung capacity commonly seen in emphysematous lungs may not result entirely from abnormal mechanical properties in the areas showing emphysema. The mechanical abnormalities may also derive from areas that appear normal, although the possible reasons for this are obscure (reviewed by Thurlbeck 1983). An alternate explanation for this discordance between elastic recoil and morphologic emphysema may be the problems of sampling and grading intrinsic to these morphologic measures.

The work of Michaels et al. (1979) introduces a further complexity to the use of pressure–volume curves as an indicator of emphysema. They found that inhalation of a bronchodilator shifted the curve of smokers in the direction of increased compliance, but had no effect in nonsmokers (Figure 26). Cessation of smoking had the same effect as a bronchodilator. These results were interpreted as indicating that smoking causes some peripheral airway units to constrict and become effectively closed. Thus, pressure–volume studies to detect early changes compatible with emphysema in smokers may give false negative results unless accompanied by studies with bronchodilators.

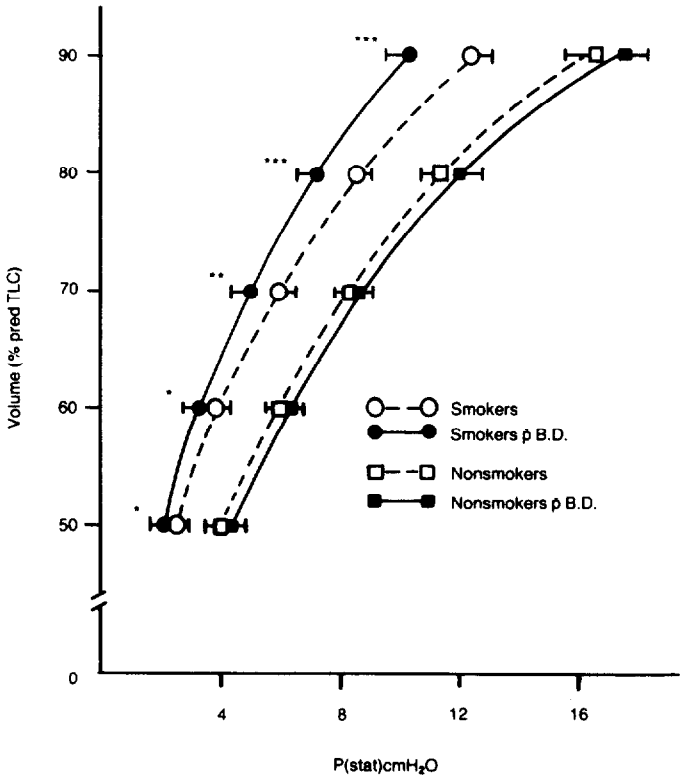

FIGURE 26.—The effect of nebulized bronchodilator on the pressure–volume characteristics of the lungs in 19 smokers (6 men and 13 women) and 16 nonsmokers (9 men and 7 women)

NOTE: The mean age was approximately 40 years (range, 19 to 56) and smokers used approximately 30 cigarettes per day. Male smokers showed borderline significant differences in indices of expiratory airflow and single breath N_2 test data as compared with the male nonsmokers, but there was no difference in these tests between female smokers and nonsmokers. As shown, smokers had significantly less elastic recoil than nonsmokers. After the bronchodilator, the difference between smokers and nonsmokers increased further, particularly at high lung volume.

B.D. = broncodilator; % pred. TLC = percent predicted total lung capacity; P(stat) = transpulmonary pressure. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$.

SOURCE: Michaels et al. (1979).

Aging and Lung Structure

With advancing age, structural and functional changes occur in the lungs of virtually all adults, even those who have no known exposure to specific inhalants through occupation or personal habits (Fishman 1982; Campbell and Lefrak 1983). The elastic recoil of the lungs declines with aging, and the residual volume to total lung capacity ratio increases. These changes are seen even in people who have never smoked, do not have signs or symptoms of cardiorespiratory disease, and have the normal (MM) phenotype of α_1-antiprotein-

ase (Knudson et al. 1977). Also with aging, the average distance between alveolar walls increases (Thurlbeck 1967a; Hasleton 1972), the proportion of lung volume that is composed of alveoli decreases, and the proportion of alveolar ducts increases (Ryan et al. 1965).

Whether the differences in the lungs that occur with aging are a consequence only of the passage of time or are the result of subtle environmental insults summed over many years is unanswerable. They are "normal" or "abnormal" depending on whether one regards "normal" as a statistical concept or as the optimal state for the tissue. In either case, the aging lung has some features similar to emphysema. Age changes alone will not, however, contribute to or obscure the diagnosis of centrilobular emphysema, which involves mainly respiratory bronchioles, recognized macroscopically as focal lesions against a background of normal lung. The age changes may overlap with early panlobular emphysema (Anderson et al. 1970). However, since smokers usually die at an earlier age than nonsmokers, aging cannot account for the differences observed between the lungs of smokers and nonsmokers at autopsy.

Emphysema and Cigarette Smoking

Studies of people and of experimental animals conclusively link cigarette smoking to the development and extent of emphysema. This information is summarized in the following discussion.

Observations in People

Post-mortem material, used to approach the problem in the 1960s and 1970s, clearly established an association between smoking and emphysema. Post-mortem lung tissue has continued to be used to study emphysema, but the main goal of recent studies has been to identify those physiologic features that correlate with emphysema rather than to quantify the relationship between smoking and emphysema. Studies of emphysema using surgically removed lung tissue, a more recent approach to studying emphysema, have aimed mainly at elucidating the physiology of the emphysematous lung. The results of these studies have involved smokers almost exclusively because of the rarity of emphysema in nonsmokers.

Studies Using Post-Mortem Material

A number of studies have examined the relationship between cigarette smoking and emphysema (Anderson et al. 1964, 1966; Thurlbeck 1963; Thurlbeck et al. 1974; Ryder et al. 1971; Auerbach et al. 1972, 1974; Spain et al. 1973). These data emphasize that not only is cigarette smoking closely associated with the development and extent of emphysema, but also it is extremely rare for the forms